

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/087862 A3

(51) International Patent Classification⁷: **C12N 15/11**,
15/85, 15/86, A61K 48/00

38106 Braunschweig (DE). **VERSCHUEREN, Kristin**
[BE/BE]; Twee Leeuwenstraat 22, Everberg, B-3078 (BE).

(21) International Application Number:
PCT/IL2004/000286

(74) Agents: **EHRlich, Gal et al.**; G.E. Ehrlich (1995) LTD.,
11 Menachem Begin Street., 52 521 Ramat Gan, (IL).

(22) International Filing Date: 29 March 2004 (29.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/458,954 1 April 2003 (01.04.2003) US

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicants (*for all designated States except US*):
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; P.O.Box 39135, Jerusalem, 91390 (IL). **GESELLSCHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG (GBF)** [DE/DE]; Mascheroder Weg1, 38124 Braunschweig (DE). **FLANDERS INTERUNIVERSITY FOR BIOTECHNOLOGY VZW (VIB)** [BE/BE]; Rijvisschestraat 120, Zwijnaarde, B-9052 (BE). **K.U. LEUVEN RESEARCH & DEVELOPMENT** [BE/BE]; Groot Begijnhof 58-59, Leuven, B-3000 (BE).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAZIT, Dan** [IL/US]; PO Box 800420, University of Virginia, Charlottesville, Virginia 22908 (US). **PELLED, Gadi** [IL/IL]; 2 Hanarkis Street, Rishon Lezion, 75424 (IL). **TURGE-MAN, Gadi** [IL/IL]; 216 Machal Street, Jerusalem, 97763 (IL). **HOFFMANN, Andrea** [DE/DE]; Koenigsberger-Ring 37, 30655 Hannover (DE). **GROSS, Gerhard** [DE/DE]; Fasanenstr. 17, 38102 Braunschweig (DE). **WODARCZYK, Claas** [DE/DE]; Heinrichstrasse 38,

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
9 September 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **TAK1-MEDIATED INHIBITION OF OSTEOGENESIS**

(57) Abstract: This invention is directed to methods, nucleic acids and compositions in TAK1-mediated regulation of SMAD activity. Promotion of TAK1 interaction with MH2 domains in SMADs negatively regulates SMAD biological activity. BMP-mediated SMAD activity is subject to TAK1 effects.



WO 2004/087862 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL04/00286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/11, 15/85, 15/86; A61K 48/00

US CL : 536/23.1; 435/325; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.1; 435/325; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIBUYA et al. Role of TAK1 and TAB1 in BMP signaling in early Xenopus development. EMBO J. February 1998, Vol. 17, No. 4, pages 1019-1028, see entire document	2,3,6-10
---		-----
Y		1,4,5,11-86
Y	MOCHIDA et al. ASK1 Inhibits Interleukin-1 induced NF-KB Activity through Disruption of TRAF6-TAK1 Interaction. J. Biol. Chem. October 2000. Vol. 275, No. 42, pages 32747-32752, see entire document	1,14,19,20,41,42
Y	YOSHIDA et al. Negative Regulation of BMP/SMAD Signaling by Tob in Osteoblasts. Cell. December 2000. Vol. 103, pages 1085-1097, see entire document	18,24,25,27-30,35-40,47-56,058-75,78-81
Y	CARNINCI et al. Normalization and Subtraction of Cap-Trapper-selected cDNAs to prepare Full-Length cDNA Libraries for Rapid Discovery of New Genes. Genome Res. October 2000. Vol. 10, pages 1617-1630, see entire document.	4,5,10-12,15,16,22,23,34,45,57,69,70,76,82-86
Y	YAMAGUCHI et al. Identification of a member of the MAPKKK Family as a potential Mediator of TGF-beta signal transduction. Science. December 1995. Vol. 270. pages 2008-2011, see entire document	4,5,10-12,15,16,22,23,34,45,57,69,70,76,82-86

☒ Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

07 July 2005 (07.07.2005)

Date of mailing of the international search report

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Ram Shukla

Telephone No. (571) 272-0735

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL04/00286

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOFFMAN et al. TGF-Beta-activated kinase-1 (TAK1), a MAP3K, interacts with SMAD proteins and interferes with osteogenesis in murine mesenchymal progenitors. J. Biol. Chem. May 2005. M5033682000, pages 1-33, see entire document	1-86

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL04/00286

Continuation of B. FIELDS SEARCHED Item 3:

EAST, STN: FILE MEDLINE

Search terms: TAK!, SMAD, BMP, MH2, IL-1, TNF, osteogenesis, proinflammatory cytokines, agonist, inhibitors